OBSTETRICS

Cerebral autoregulation in different hypertensive disorders of pregnancy

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OBJECTIVE: Cerebrovascular complications that are associated with hypertensive disorders of pregnancy (preeclampsia, chronic hypertension [CHTN], and gestational hypertension [GHTN]) are believed to be associated with impaired cerebral autoregulation, which is a physiologic process that maintains blood flow at an appropriate level despite changes in blood pressure. The nature of autoregulation dysfunction in these conditions is unclear. We therefore evaluated autoregulation in 30 patients with preeclampsia, 30 patients with CHTN, and 20 patients with GHTN and compared them with a control group of 30 normal pregnant women.

STUDY DESIGN: The autoregulatory index (ARI) was calculated with the use of simultaneously recorded cerebral blood flow velocity in the middle cerebral artery (transcranial Doppler ultrasound), blood pressure (noninvasive arterial volume clamping), and end-tidal carbon dioxide during a 7-minute period of rest. ARI values of 0 and 9 indicate absent and perfect autoregulation, respectively. We use analysis of variance with Bonferroni test vs a control group. Data are presented as mean ± standard deviation.

RESULTS: ARI was significantly reduced in preeclampsia (ARI, 5.5 ± 1.6; $P = .002$) and CHTN (ARI, 5.6 ± 1.7; $P = .004$), but not in GHTN (ARI, 6.7 ± 0.8; $P = 1.0$) when compared with control subjects (ARI, 6.7 ± 0.8). ARI was more decreased in patients with CHTN who subsequently experienced preeclampsia than in those who did not (ARI, 3.9 ± 1.9 vs 6.1 ± 1.2; $P = .001$). This was not true for women with GHTN or control subjects who later experienced preeclampsia.

CONCLUSION: Pregnant women with CHTN or preeclampsia (even after exclusion of superimposed preeclampsia) have impaired autoregulation when compared with women with GHTN or normal pregnancy. Whether the decreased ARI in patients with CHTN who later experience preeclampsia is due to preexistent differences or early affected cerebral circulation remains to be determined.

Key words: cerebral autoregulation, hypertension, preeclampsia, pregnancy, transcranial Doppler

Cite this article as: van Veen TR, Panerai RB, Haeri S, et al. Cerebral autoregulation in different hypertensive disorders of pregnancy. Am J Obstet Gynecol 2015;212:513.e1-7.

Hypertension is one of the most common medical complications of pregnancy, accounting for 16-38% of all maternal deaths.[1,2] Although multiple maternal organs can be affected, cerebrovascular involvement is one of the more serious because it can lead to death or long-term morbidity because of cerebrovascular hemorrhage or edema.[1,2] The cerebral manifestations in these patients are similar to those that are seen in the posterior reversible encephalopathy syndrome,[3,4] which is hypothesized to be related to impaired autoregulation and which leads to either over- or underperfusion of the brain.[3,5,6]

Hypertensive disorders of pregnancy range in a spectrum from chronic hypertension (CHTN) to gestational hypertension (GHTN), preeclampsia, and super-imposed preeclampsia (SiPE) in the setting of CHTN. Women with CHTN have an increased risk of the development of SiPE. The incidence has been reported to be from 12-29%,[7-9] although women with severe CHTN in the first trimester have been reported to go on to SiPE in up to 52% of cases.[10] The risk for cerebrovascular complications during pregnancy is increased with all hypertensive disorders[11-13] but is most pronounced with severe preeclampsia and SiPE.[12,13] These complications are believed to be caused by impaired cerebral autoregulation, which is related to endothelial dysfunction.[14]

Cerebral autoregulation is the ability of the cerebral vasculature to maintain adequate cerebral perfusion despite changes in blood pressure. The cerebral autoregulation can be assessed by the use of a combination of transcranial Doppler (TCD) imaging and continuous noninvasive blood pressure measurement.[15]

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Received Sept. 7, 2014; revised Oct. 12, 2014; accepted Nov. 1, 2014.

The authors report no conflict of interest.

Presented at the 34th annual meeting of the Society for Maternal-Fetal Medicine, New Orleans, LA, Feb. 3-8, 2014.

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0002-9378/$36.00 • http://dx.doi.org/10.1016/j.ajog.2014.11.003

The functionality of the autoregulation can be expressed as the autoregulatory index (ARI), with 0 being absent and 9 perfect cerebral autoregulation.[16] This ARI has been shown to be lower in preeclampsia when compared with normotensive control subjects.[5] The ARI was independent of blood pressure and clinical symptoms, which may explain the reason that cerebral complications such as eclampsia and cerebrovascular hemorrhage can occur without sudden and/or excessive elevation in blood pressure.[5] The ARI of the other hypertensive disorders in pregnancy is not known. Based on the increased risks of cerebrovascular complications that are seen in pregnancies that are complicated by CHTN and preeclampsia, but not in GHTN, we hypothesize that the autoregulation is impaired in CHTN (as has been shown for preeclampsia), but not in GHTN.

Consequently, the aim of this study was to evaluate cerebral autoregulation in hypertensive disorders of pregnancy (SiPE, preeclampsia, CHTN, and GHTN) and to compare this with a control group of normal pregnant women. Furthermore, we measured the more traditional parameters of cerebral blood flow velocity (CBFV), critical closing pressure (CrCP), and resistance-area-product to gain additional insight in the pathophysiologic condition.

Materials and Methods

We conducted a prospective cohort study in nonlaboring pregnant women who were recruited at 20-41 weeks' gestation. The Institutional Review Boards at Baylor College of Medicine in Houston, TX, and North Austin Medical Center in Austin, TX, approved this study; informed consent was obtained from each participant before data collection.

Patients were recruited and tested at Texas Children's Pavilion for Women in Houston and North Austin Maternal-Fetal Medicine in Austin, TX, either at the time of admission to the hospital for treatment of a hypertensive disorder or at the time of routine prenatal care. Inclusion criteria were maternal age >18 years and absence of a history of cerebrovascular disease or epilepsy. Hypertensive diagnoses were based on American College of Obstetricians and Gynecologists guidelines.[17,18] Exclusion criteria consisted of smoking, drug use, and the initiation of antihypertensive therapy or treatment with magnesium sulfate <48 hours before the examination.

With the use of a standard data collection sheet, demographic characteristics and obstetrics data were abstracted from patient interviews and medical records. The following maternal characteristics were based on self-report: race/ethnicity, height, current and prepregnancy weight, smoking, alcohol, and illicit substance use. Gestational age was determined by menstrual dating. In cases of uncertain menstrual dates, ultrasound estimates of gestational age were used. Patients were followed until 6 weeks after delivery.

At time of TCD examination, brachial systolic and diastolic blood pressures were measured. With the patients in semi-Fowlers position, bilateral maternal TCD examinations of the middle cerebral artery were carried out with the use of 2-MHz pulsed, range-gated TCD probes (Spencer Technologies, Seattle, WA) that were held in place with the use of a head frame.

Blood pressure was measured continuously noninvasively with finger arterial volume clamping (Finometer Pro; Finapres Medical Systems, Amsterdam, the Netherlands) with the servo-adjust switched off and was afterwards calibrated with the brachial blood pressure. The blood pressure tracing also served to mark each cardiac cycle. End-tidal CO_2 was measured with a nasal cannula (Nellcor Oximax N-85; Covidien, Mansfield, MA), and linearly interpolated at the end of each expiratory phase.

Patients were measured only once for a period of 7 minutes. All data were recorded at 50 Hz, interpolated to 200 Hz, and visually inspected during analysis to remove large spikes. A median filter was used to remove small spikes and artifacts in the CBFV signal. All signals were then low-pass filtered with a Butterworth filter with a cutoff frequency of 20 Hz.[19] Mean blood pressure, bilateral CBFV, end-tidal CO_2, and heart rate were then calculated for each beat. The CrCP and resistance-area product (RAP) were obtained with the use of the first harmonic of blood pressure and CBFV of each cardiac cycle.[20] All signals were then resampled at 5 Hz.[19]

Cerebral autoregulation was determined from the CBFV responses to spontaneous fluctuations in mean arterial blood pressure, as described previously.[19] Segments of 512 samples and 50% superposition were transformed with the fast Fourier transform algorithm, with the use of the Welch method, to obtain the transfer function parameters coherence, gain, and phase in the low frequency range (<0.1 Hz). The inverse fast Fourier transform was then performed to estimate the impulse and step responses. The CBFV step response to a sudden change in blood pressure was compared with 10 template curves proposed by Tiecks et al[16] and the best-fit curve that corresponded to the ARI. An ARI value of 9 represents the best observed cerebral autoregulation.[16]

Measurements were rejected if coherence did not reach 0.5 for any frequency <0.25 Hz. Reported baseline CBFV, blood pressure, RAP, and CrCP were the averages over the 7-minute baseline recording.

All data sets were checked for normalcy of distribution (Sigmastat 2004; Systat Software, Richmond, CA). Data are reported as mean and standard deviation or median with the corresponding range, as appropriate. Analyses were performed with analysis of variance with Bonferroni's post-hoc test, analysis of variance on ranks with Dunn's post hoc test (both comparisons vs the control group), and a second analysis that used multiple linear regression that included prepregnancy body mass index and gestational age at study that was performed to control for these potential confounders.

χ^2 without Yates correction was used for analysis between groups. The Student *t* test or Mann-Whitney Rank Sum test were used for subgroup analysis. Univariate regression analysis was used to

TABLE 1
Demographic data

Variable	Preeclampsia (n = 30)	Chronic hypertension (n = 30)	Gestational hypertension (n = 20)	Control subjects (n = 30)	*P* value[a]
Maternal age, y[b]	30 ± 7	29 ± 6	31 ± 5	30 ± 6	.83
Pregestational body mass index, kg/m^2[b]	29 ± 8	36 ± 9[c]	31 ± 8	31 ± 5	< .001
Diabetes mellitus, n (%)	6 (20)	6 (20)	2 (10)	0	.061
Type 2	2 (7)	2 (7)	0	—	
Gestational	4 (13)	4 (13)	2 (10)	—	
Twin pregnancy, n (%)	5 (17)	0	3 (15)	2 (7)	.11
Nulliparous, n (%)	23 (77)[d]	11 (37)	12 (60)	17 (57)	.020
Estimated gestational age, wk[e]					
At study	35^4 (24^1–40^1)	33^4 (20 –38^2)[d]	37^1 (27^6–38^6)	36^0 (23^3–40^3)	.002
At delivery	35^6 (24^3–40^2)[d]	37^2 (24^4–39^1)[d]	38^0 (28^6–39^0)[d]	39^1 (33^4–41^0)	< .001

[a] Analysis of variance on ranks or chi-square; [b] Data are given as mean ± standard deviation; [c] $P < .001$ vs control (analysis of variance with Bonferroni test); [d] $P < .05$ vs control (analysis of variance on ranks with Dunn's test); [e] Data are given as median (range).

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assess the relationship between autoregulation parameters and blood pressure. A 2-tailed probability value of < .05 was used to indicate statistical significance.

Results

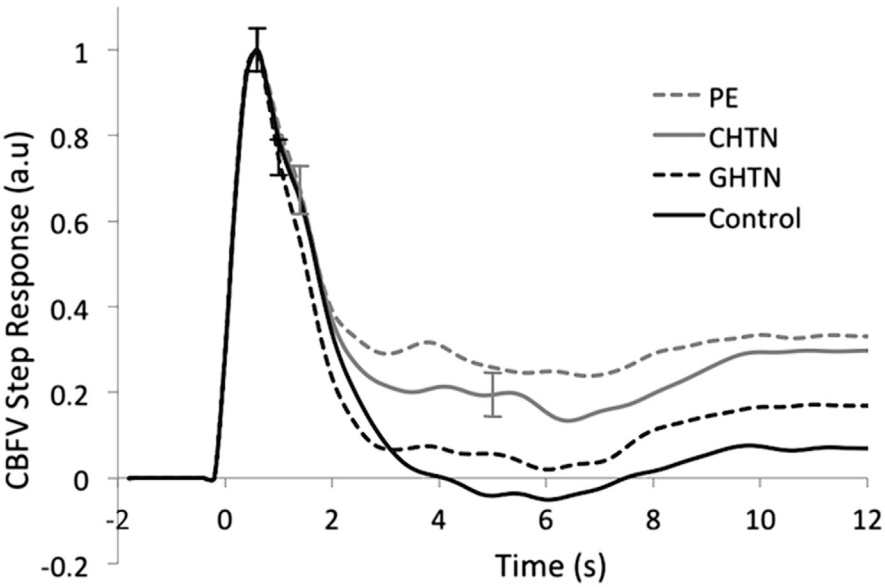
A total of 30 patients with preeclampsia (new onset, 23; SiPE, 7 [confirmed preeclampsia at the time of measurement]), 30 patients with CHTN (with antihypertensive treatment, 16; without antihypertensive treatment, 14), 20 patients with GHTN, and 30 control subjects were enrolled. Of the women with CHTN who had undergone antihypertensive therapy, 12 women used only labetalol, and 2 women had labetalol combined with either hydralazine/furosemide or nifedipine. The other 2 women received metoprolol for blood pressure control.

Seven patients (23%) with CHTN (5 women with and 2 women without medication), 3 patients (10%) in the control group, and 5 patients (25%) with GHTN later experienced preeclampsia.

Maternal demographics were similar for both groups, except for gestational age at examination and delivery, pregestational body mass index, and parity (Table 1).

Women with preeclampsia/SiPE (ARI, 5.5 ± 1.6) or CHTN (ARI, 5.6 ± 1.7) had a significantly lower ARI than the control group (ARI, 6.7 ± 0.8); GHTN (ARI, 6.7 ± 0.8) was not associated with an altered ARI (Figure 1, Table 2). There was no

FIGURE 1
Average CBFV step responses of all groups



Error bars represent largest ± standard error of the mean.

a.u, arbitrary unit; *CBFV*, cerebral blood flow velocity; *CHTN*, chronic hypertension; *GHTN*, gestational hypertension; *PE*, preeclampsia.

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TABLE 2
Hemodynamic data

Variable	Preeclampsia (n = 30)/ New preeclampsia (n = 23)/Superimposed preeclampsia (n = 7)	Chronic hypertension (n = 30)/No later preeclampsia (n = 23)/ Later preeclampsia (n = 7)	Gestational hypertension (n = 20)/No later preeclampsia (n = 15)/ Later preeclampsia (n = 5)	Control subjects (n = 30)/ No later preeclampsia (n = 27)/Later preeclampsia (n = 3)	*P* value[a]
Autoregulation index[b]	5.5 ± 1.6[c]/6.0 ± 1.1/3.9 ± 2.2[d]	5.6 ± 1.7[c]/6.1 ± 1.2/3.9 ± 1.9[d]	6.7 ± 0.8/6.7 ± 1.0/6.9 ± 0.3	6.7 ± 0.8/6.6 ± 0.8/7.2 ± 0.3	< .001
Mean arterial pressure, mm Hg[b]	103 ± 13[e]/101 ± 12/111 ± 14	94 ± 12[e]/92 ± 12/100 ± 11	100 ± 11[e]/98 ± 11/107 ± 6	83 ± 10/82 ± 10/91 ± 10	< .001
End-tidal CO_2, mm Hg[b]	33 ± 2/33 ± 2/34 ± 2	33 ± 2/33 ± 2/33 ± 3	34 ± 1/34 ± 1/33 ± 1[f]	33 ± 2/33 ± 2/34 ± 0.3	.40
Mean cerebral blood flow velocity, cm/sec[b]	86 ± 32[e]/78 ± 16/113 ± 55[f]	69 ± 11/68 ± 11/71 ± 11	68 ± 11/68 ± 12/71 ± 6	68 ± 9/67 ± 9/76 ± 5	< .001
Critical closing pressure, mm Hg[g]	5 (0–40)/9 (0–40)/1 (0–34)	14 (0–35)/15 (0–35)/7 (0–33)	7 (0–34)[h]/7 (0–34)/10 (2–14)	16 (0–26)/15 (0–26)/21 (12–23)	.012
Resistance area product, mm Hg × sec × cm^{-1}[b]	1.29 ± 0.37[i]/1.21 ± 0.33/ 1.55 ± 0.41[f]	1.17 ± 0.36/1.13 ± 0.35/ 1.28 ± 0.40	1.39 ± 0.25[c]/1.37 ± 0.28/ 1.42 ± 0.08	1.05 ± 0.22/1.06 ± 0.23/0.96 ± 0.20	.001
Time study to preeclampsia diagnosis, d[g]		15 (4–108)	5 (2–14)	35 (10–78)	.12

[a] Adjusted for body mass index and gestational age at measurement; [b] Data are given as mean ± standard deviation; [c] $P < .01$ vs control subjects (analysis of variance with Bonferroni test); [d] $P < .01$ vs new preeclampsia or no later preeclampsia (*t*-test or Mann-Whitney *U* test); [e] $P \leq .001$ vs control subjects (analysis of variance with Bonferroni test); [f] $P < .05$; [g] Data are given as median (range); [h] $P < .05$ (analysis of variance on ranks with Dunn's test); [i] $P < .05$ vs control.

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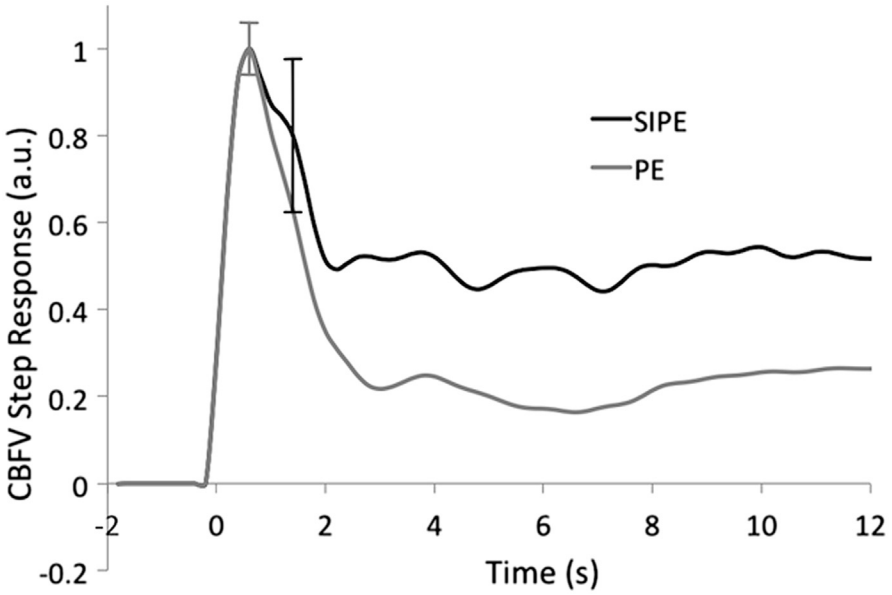
FIGURE 2
Average CBFV step responses of the preeclampsia group



The group was subdivided into superimposed preeclampsia and preeclampsia. *Error bars* represent largest ± standard error of the mean.

a.u., arbitrary unit; *CBFV*, cerebral blood flow velocity; *PE*, preeclampsia; *SiPE*, superimposed preeclampsia.

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difference in ARI between women with CHTN with and without medication (ARI, 5.4 ± 1.9 vs 5.8 ± 1.4, respectively; $P = .55$). These outcomes did not change after adjustment for prepregnancy body mass index and gestational age at the time of study.

The ARI of women with SiPE was significantly lower than for those women with new onset preeclampsia (ARI, 3.9 ± 2.2 vs 6.0 ± 1.1, respectively; $P = .002$; Figure 2), but the ARI in new onset preeclampsia was still decreased when compared with the control group (ARI, 6.0 ± 1.1 vs 6.7 ± 0.8, respectively; $P = .007$). RAP was significantly higher in preeclampsia and GHTN than in the control subjects and even higher in the patients with SiPE. CrCP was lower in women with GHTN than in control subjects; however, although there was a trend to a lower CrCP in preeclampsia, this difference did not reach significance.

ARI, RAP, and CrCP were not associated significantly with mean arterial blood pressure in women with preeclampsia. However, in both CHTN and control pregnant women, blood pressure was associated positively with RAP ($P < .0001$ and $P = .014$, respectively). Women with GHTN demonstrated a mean arterial blood pressure positive association with CrCP and ARI ($P = .026$ and $P = .037$, respectively).

In subgroup analysis of women who did or did not experience preeclampsia (Table 2), the ARI was significantly lower in women with CHTN who subsequently experienced SiPE vs those that did not. This was not seen in the GHTN group or control subjects. The time between the measurements and the development of preeclampsia varied widely but was not different among the 3 groups (Table 2).

Comment

In this study, we examined the autoregulation functionality in different hypertensive states of pregnancy and compared them with those that were seen in pregnant normotensive control subjects. Our findings indicate that cerebral autoregulation is impaired in pregnant women with CHTN and preeclampsia and even more so in patients with SiPE. Cerebral autoregulation is, however, independent from the actual blood pressure values. Furthermore, the functionality of autoregulation is impaired in pregnant women with CHTN, who subsequently experienced SiPE when compared with women who did not experience SiPE. These results may explain the reason that women with CHTN or preeclampsia have an increased risk of the development of cerebral complications or stroke during pregnancy, even without sudden or excessive elevation in blood pressure.[11-13]

Previous studies also have shown abnormal cerebral hemodynamics in preeclampsia, SiPE, and CHTN[6,21-23] and have interpreted the finding of increased cerebral perfusion pressure or CBFV as impaired autoregulation. However, none of these studies measured CBFV and blood pressure simultaneously and therefore could not assess the dynamic cerebral autoregulation. More recently, our group demonstrated decreased ARI in women with preeclampsia when compared with normotensive control subjects,[5] with the largest degree of impairment in women with SiPE who required ≥2 antihypertensive drugs to control their blood pressure. In this study, we also found a significant difference between SiPE and new onset preeclampsia. Indeed, the ARI of patients with new onset preeclampsia was not much different from the ARI of patients with CHTN (ARI, 5.9 ± 1.3 vs 5.6 ± 1.7, respectively; $P = .48$). But in both groups, the large range in ARI indicates nonhomogeneity in disease severity and possibly pathophysiologic condition. In addition, women with CHTN who subsequently experienced SiPE had a significantly lower ARI than those who did not progress to this disease; the ARIs in the GHTN and control groups were similar for those who did and did not progress to preeclampsia.

The spectrum of conditions (which ranged from SiPE, preeclampsia, and CHTN to GHTN and control subjects), along with their associated spectrum in ARI, might reflect a range of endothelial impairment. Scientific evidence suggests that altered expression of angiogenic factors produces systemic endothelial dysfunction and plays an

important role in the pathogenesis of preeclampsia.[14] The extent of these deviations depends on the type of hypertensive disorder, which is more pronounced in preeclampsia than in women with CHTN and GHTN when compared with control subjects.[24-26] Another study found an altered angiogenic balance in preeclampsia, but not in GHTN.[27] These results are in agreement with our study. We also found that the ARI was lowest in the preeclampsia group; the ARI in women with GHTN was similar to the control group. The proteinuria that is seen in preeclampsia is caused by renal endothelial dysfunction and is also related to this angiogenic inbalance.[14]

The increase in RAP that was seen in women with GHTN and preeclampsia is in accordance with a previous study, which suggests that RAP might reflect myogenic activity.[28] Interestingly, CrCP, which is more indicative of metabolic control,[28] appears to be decreased in both preeclampsia and GHTN, which counteracts the effect of RAP and suggests an abnormal neurovascular coupling, which was also seen in former (pre)eclamptic women.[29] Further work is required to establish the interpretation and significance of this difference.

Women with CHTN who subsequently did experience SiPE had a significantly decreased ARI. Their ARI was comparable with patients who already had SiPE. This can be explained in 2 possible ways: first, it is possible that the changes in cerebral autoregulation occur before clinical symptoms of SiPE appear, which reflects early manifestation of disease or the underlying pathophysiologic condition. This possibility is further supported by the finding that CHTN outside of pregnancy does not appear to alter cerebral autoregulation, even in sustained untreated middle-aged and older people.[30-32] Furthermore, previous research has demonstrated that decreased maternal middle cerebral artery resistance in the second trimester was predictive of subsequent preeclampsia in low-risk pregnant women who can be expected to have no endothelial dysfunction at the time of the TCD examination.[33] These findings, coupled with evidence that angiogenic factors have been detected in maternal serum 5-10 weeks before the onset of preeclampsia, suggest that ARI may indeed be impaired in these cases well before the clinical manifestation of disease.[14,24,27] If this is in fact true, the ARI could have the potential of being used as a screening tool.

Second, the reduced ARI is an indication of baseline endothelial dysfunction, which makes pregnant women with CHTN more susceptible for the development of SiPE. This is supported by the fact that women with CHTN or diabetes mellitus experience preeclampsia at a lower level of angiogenic disturbance[25] and would also explain the reason that the ARI in women with GHTN and control subjects was normal. In CHTN, endothelial function is already impaired, and the angiogenic imbalance causes a second hit and SiPE. This theory is in agreement with Noori et al,[27] who found impaired endothelial function in the brachial artery before angiogenic factors were altered.

One of the strengths of this study is the inclusion of patients with multiple hypertensive disorders of pregnancy and a pregnant control group, who were all studied in an identical setting. Further, none of the women received magnesium sulfate or had recent changes in antihypertensive therapy at time of the measurement.

This study also has some limitations that merit discussion. A limitation of the use of TCD is that only the CBFV can be obtained and therefore relies on the assumption that changes in CBFV are directly proportional to changes in CBF. The data only represent a 7-minute period. Although the reliability of the method has been proved in a longitudinal fashion in nonpregnant subjects, this might not hold true for preeclampsia, during which blood pressures can be very labile. The study has a small sample size, predominantly in the SiPE, and GHTN groups, and in the comparison of those who did vs did not experience preeclampsia later during their pregnancy, which precluded any detailed subgroup analysis on severity of preeclampsia, laboratory abnormalities, or neurologic symptoms. The incidence and severity of adverse events in CHTN is related to the duration of the disease and the severity and control of the hypertension,[7] but we do not have information on this from our patients. Finally, the women with CHTN had a significant higher pregestational body mass index and were studied at a younger gestational age; however, controlling for this possible confounder in a multiple regression analysis did not change the results.

In conclusion, our findings suggest the presence of impaired dynamic cerebral autoregulation in patients with preeclampsia, particularly in those with SiPE, when compared with their GHTN or normotensive counterparts. The autoregulation is impaired in patients with CHTN who subsequently experience SiPE, but not in normotensive pregnant women or women with GHTN who subsequently experience preeclampsia. Whether this disparity is due to preexistent differences or early affected cerebral circulation in pregnant women with CHTN remains to be determined. ■

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